JACC Vol. 11, No. 5
May 1988:917–24

CLINICAL STUDIES

Analysis of Morbid Events and Risk Factors for Death After Cardiac Transplantation

JAMES K. KIRKLIN, MD, FACC, DAVID C. NAFTEL, PhD, DAVID C. McGIFFIN, MD, REBA F. McVAY, RN, EUGENE H. BLACKSTONE, MD, FACC, ROBERT B. KARP, MD, FACC
Birmingham, Alabama

Risk factors for death after cardiac transplantation performed at the University of Alabama at Birmingham from January 1981 to July 1985 included (by multivariate analysis) higher calculated preoperative pulmonary vascular resistance (early and constant phases), morphology of cardiomyopathy (versus ischemic heart disease) (constant phase only) and black race (constant phase). Overall actuarial survival was 71% at 1 year and 48% at 3 years (including azathioprine and cyclosporine eras). The hazard function for death was highest immediately after operation and declined rapidly thereafter, merging with a constant phase of risk at about 3 months.

The most favorable group for long-term survival was the group of white patients with ischemic heart disease and low pulmonary vascular resistance. When such patients had a pulmonary vascular resistance <3 units·m², the 3 year survival rate exceeded 85%. The most common causes of death were acute rejection (24%) and infection (17%). The risk of infection remained highest during the first several months after any period of augmented immunosuppression.

(J Am Coll Cardiol 1988;11:917–24)

Cardiac transplantation is currently an accepted therapy for intractable end stage heart disease. Because the supply of donor hearts is limited, analysis of morbid events and identification of the risk factors for premature death early and late after cardiac transplantation could have an important role in identifying patients most likely to derive benefit from cardiac transplantation. This study was undertaken to further evaluate new knowledge and techniques that could improve the results of cardiac transplantation.

Methods

Study patients. Between 1981 (first cardiac transplantation on November 24, 1981) and July 1985, 63 patients underwent cardiac transplantation at the University of Alabama at Birmingham. This was an era of ready availability of donor hearts and of exploration of the role of cardiac transplantation among the therapeutic modalities of advanced heart disease. Of these 63 patients, 60 underwent primary orthotopic cardiac transplantation and 3 underwent heterotopic transplantation. Six of the 63 patients underwent a second cardiac transplantation and 1 underwent a third transplantation. The primary diagnosis was idiopathic cardiomyopathy in 42 patients (in 2, cardiomyopathy was associated with valvular heart disease), ischemic cardiomyopathy in 18 and uncorrectable congenital heart disease in 3. The first 17 patients underwent cardiac transplantation with azathioprine-based immunosuppression, and the subsequent 46 patients with cyclosporine-based immunosuppression.

Donor heart procurement. Hearts were procured from local, regional and distant areas throughout this experience. The mean donor heart ischemic time was 148 minutes (range 47 to 253). Standard criteria were used in selecting appropriate donor hearts (1–3).

Operative technique. One liter of cold crystalloid hyperkalemic (30 mEq/liter) cardioplegic solution was infused at the time of donor heart harvesting. Topical cooling and storage in cold saline solution (5 to 6°C) were employed during transportation. During implantation, hypothermic (25 to 28°C) cardiopulmonary bypass was utilized, and topical cardiac hypothermia was maintained with intermittent irrigation of the pericardial space with cold saline solution. Cardioplegic reinfusion was not employed during implantation. Orthotopic transplantation was performed by the tech-

From the Department of Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham School of Medicine and Medical Center, Birmingham, Alabama.

Manuscript received September 4, 1987; revised manuscript received November 24, 1987, accepted December 2, 1987.

Address for reprints: James K. Kirklin, MD, Department of Surgery, University of Alabama at Birmingham, University Station, Birmingham, Alabama 35294.

0735-1097/88/$3.50

nique described by Lower and Shumway (4), and heterotopic cardiac transplantation by that described by Barnard, Novitsky and their colleagues (5,6).

Immunosuppression. *Azathioprine-based immunosuppression* included azathioprine at a dose of 2 mg/kg body weight preoperatively and a postoperative dose of 2 mg/kg per day adjusted according to the white blood cell count. Methylprednisolone was administered intraoperatively (500 mg at the conclusion of cardiopulmonary bypass) and postoperatively (125 mg every 8 h for three doses). Prednisone was initiated at a daily dose of 1 mg/kg and gradually tapered over 2 months to a dose of 0.2 mg/kg per day. Rabbit antithymocyte globulin was administered for 10 to 14 days after transplantation.

Cyclosporine-based immunosuppression included the same protocols for methylprednisolone and prednisone. Cyclosporine was administered at a dose of 10 to 12 mg/kg orally before transplantation, and doses were adjusted postoperatively to maintain a whole blood cyclosporine level (by radioimmunoassay) of 500 to 1,000 ng/ml. After 3 months, the level was gradually reduced to 250 to 500 ng/ml. Triple drug therapy with cyclosporine, azathioprine and prednisone was not employed during this time period.

Rejection. Rejection episodes were identified in nearly all cases by endomyocardial biopsy and the patients were treated with transient augmentation of immunosuppression. In patients given cyclosporine, rejection graded as moderate or severe on biopsy (7,8) always preceded treatment.

Rejection was treated initially with intravenous methylprednisolone, (1 g) daily, for 3 days. Antithymocyte globulin was generally added if rejection 1) persisted (as assessed by endomyocardial biopsy) after two courses of methylprednisolone therapy, or 2) was accompanied by hemodynamic derangements. A rejection episode was considered to have ended when rejection was absent or mild on biopsy. Two episodes separated by only several days were considered as one continuous rejection episode.

Infection. Any infective episode requiring hospitalization or intravenous antibiotic agents or having the potential of fatal outcome was considered a major infection.

Cardiac failure. A clinical event associated with signs of either low cardiac output or symptomatic pulmonary venous hypertension was termed acute cardiac failure. In addition, measured cardiac index <2.0 liters/min per m^2 or the need for greater inotropic support than that provided by dopamine during the first week after transplantation was termed acute cardiac failure. Subacute cardiac failure was defined as low cardiac output with or without pulmonary venous hypertension, documented by repeated right heart catheterization and lasting weeks or months.

Sudden death. Death was defined as sudden if it occurred unexpectedly and without identifiable preceding signs of acute cardiac failure, usually while the patient was out of the hospital.

Renal failure. Renal failure was defined by serum creatinine levels >2.0 mg/100 ml or the need for dialysis, or both.

Definition of postoperative events. A cause of death was assigned to each patient who died during the study period. Whenever possible, the assigned cause was based on autopsy findings; when these were not available, a cause was assigned after review of all clinical, biopsy and culture information available before death. Events associated with morbidity (morbid events) were identified for each patient over the period of follow-up study. Deaths occurring during a morbid event (but not necessarily caused by that event) were also tabulated.

Pulmonary vascular resistance. Calculation of the pulmonary vascular resistance (PVR) index (units·m^2) was made by the following formula:

$$\frac{\text{Mean pulmonary artery pressure} - \text{Left atrial pressure}}{\text{Cardiac index}} = \text{PVR}.$$

Mean pulmonary artery (PA) pressure was determined electronically or by the formula: PA mean = PA diastolic + [(PA systolic − PA diastolic)/3]. If left atrial pressure was not available, the pulmonary capillary wedge pressure was used. The value used in all analyses was that obtained closest to the time of transplantation without specific attempts at modification by vasodilator therapy.

Follow-up studies. All surviving patients were seen periodically in follow-up, except for two patients who underwent long-term follow up in another institution. Additional details were obtained by correspondence with the patients' physician. Follow-up was completed through December 31, 1985 for all morbid events and through July 1, 1986 for survival.

Data analysis. The usual contingency tables and methods for estimating the likelihood that differences were due to chance were used. Survival and freedom from other adverse events were described in a time-related manner actuarially, parametrically and by a depiction of the instantaneous risk of the event at all points in time after the operation (9). Factors that increased the risk of death were identified by multivariate analysis in the hazard domain. The variables entered in the risk factor analysis for death are given in the Appendix.

Results

Survival. Among the 63 patients, 29 deaths occurred by July 1, 1986. The actuarial survival was 71, 51 and 48% at 1, 2 and 3 years after transplantation, respectively (Fig. 1). The hazard function for death was highest immediately after operation and declined rapidly thereafter to merge with the constant phase of hazard by about 3 months postoperatively (Fig. 2).

Causes of death (Table 1). The most common causes of death were acute cardiac rejection and infection, which accounted for 41% of the deaths. Four of the six patients who died intraoperatively developed irreversible right ven-

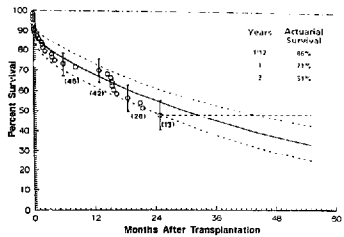

Figure 1. Survival after 63 cardiac transplantations. **Circles** represent individual patient deaths in the actuarial curve. **Vertical bars** represent the 70% confidence limits of the actuarial estimate. The **numbers in parentheses** represent the number of patients at risk in the time interval. The **longer dashed lines** extend to the point of longest follow-up. The **solid line** is the parametric estimate of event-free survival. The **shorter dashed lines** enclose the parametric 70% confidence limits around the event-free estimate. The **dot-dash-dot line** represents survival in the age-race-gender–matched general population (U.S. Life Tables, 1976).

tricular failure in the setting of marked intraoperative (n = 1) or preoperative (n = 3) pulmonary hypertension. Two of the six patients died with acute cardiac failure associated with destabilizing intraoperative bleeding. One of these, who underwent heterotopic transplantation, had severe bleeding through the interstices of the tube graft to the pulmonary artery; the other, with uncorrectable congenital heart disease, had undergone seven previous cardiothoracic operations including a modified Fontan procedure.

Risk factors for death (Table 2). Immunologic intolerance of the transplanted heart is obviously the most powerful risk factor for death. However, among the preoperative variables

Figure 2. Hazard function (instantaneous risk of the event at all points in time after operation) for death after 63 cardiac transplantations. The **dashed lines** enclose the 70% confidence limits. The **dot-dash-dot line** (first above the abscissa) represents the hazard function in the matched general population.

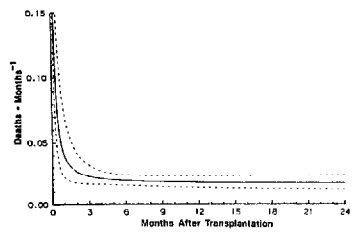

Table 1. Causes of Death in 29 of the 63 Patients Undergoing Cardiac Transplantation

Cause of Death	No.	%
Acute rejection	7	24
Infection	5	17
Aspergillus pneumonia	2	
Disseminated CMV	1	
CNS fungal infection	1	
Perforated duodenal ulcer with Serratia sepsis	1	
Intraoperative right ventricular failure	4	14
Intraoperative bleeding	2	7
Chronic rejection	2	7
Pulmonary embolism	2	7
Sudden death (unexplained)	2	7
Unexplained acute cardiac failure	1	3
Subacute cardiac and renal failure	1	3
Pancreatitis	1	3
Acute neurologic event	1	3
Chronic pulmonary failure	1	3
Total	29	

CMV = cytomegalovirus; CNS = central nervous system.

available for multivariate analysis, only three were identified with reasonable certainty ($p \leq 0.1$) as being risk factors: high pulmonary vascular resistance, black race and morphology of cardiomyopathy. The effect of pulmonary vascular resistance was also evident on simple analysis (Fig. 3). White patients with ischemic heart disease and low pulmonary vascular resistance are predicted to have the most favorable intermediate-term survival after cardiac transplantation (Fig. 4). Such patients with a pulmonary vascular resistance ≤ 3 units·m^2 had greater than 85% chance of surviving 3 years after transplantation.

The immunosuppressive era was not a risk factor on multivariate analysis, but patients undergoing orthotopic transplantation who were maintained on cyclosporine and prednisone (without conversion to azathioprine or discontinuation of cyclosporine) had an actuarial survival rate of 79% at 1 year and 68% to 2 years of follow-up, which was nearly

Table 2. Risk Factors for Death After Cardiac Transplantation

Incremental Risk Factors for Death	Hazard Phase: Early p Value	Hazard Phase: Constant p Value
Clinical: higher pulmonary vascular resistance (Wood units · m^2)*	0.004	0.005
Demographic: black race		0.008
Morphologic: cardiomyopathy		0.07

*Substitution of pulmonary vascular resistance in *Wood units* in the analysis provided a significant but higher p value in both the early and constant phase. The shaping variables and coefficients are listed in the Appendix.

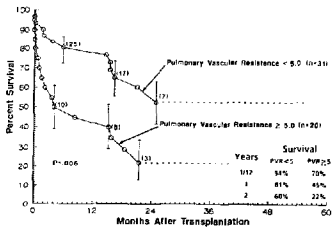

Figure 3. Actuarial survival after 63 cardiac transplantations according to preoperative pulmonary vascular resistance (PVR) (Wood units·m²). In 12 patients, the preoperative pulmonary vascular resistance could not be retrospectively ascertained. **Dashed lines** indicate the longest point of follow-up. The value for difference = 0.01.

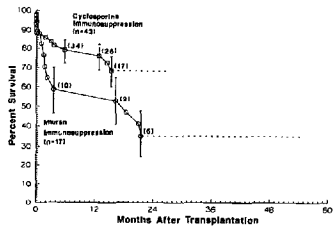

Figure 5. Actuarial survival for 60 patients undergoing orthotopic cardiac transplantation, with follow-up to July 1986. **The upper curve** represents 43 patients maintained on cyclosporine immunosuppression. Patients are censored at discontinuation of cyclosporine. **The lower curve** represents 17 patients maintained on azathioprine (Imuran) immunosuppression. The individual **circles** and **squares** represent individual patients undergoing an event. **The numbers in parentheses** represent the number of patients at risk in the time interval. **Dashed lines** indicate the duration of longest follow-up. **The p value** for difference = 0.15.

twice the 2 year survival rate for azathioprine-treated patients (p = 0.15) (Fig. 5).

A small group (n = 11) of patients who originally received cyclosporine were, because of chronic renal dysfunction after cardiac transplantation, later treated with azathioprine with complete cessation of cyclosporine and doubling of maintenance dose of prednisone (for 3 months). This group had a high subsequent mortality rate, with four patients (36%; confidence limits 19 to 56%) dying within 1 year after conversion.

Heterotopic cardiac transplantation was performed in only three patients, in all three because of severe preoperative pulmonary hypertension. Two died within 6 months of transplantation, and the other is well 2 years after transplantation.

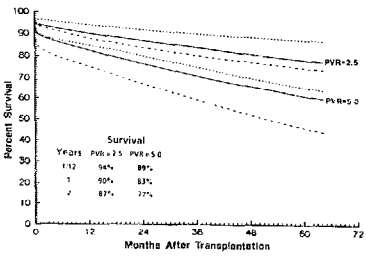

Figure 4. Survival after 63 cardiac transplantations correlated with pulmonary vascular resistance (PVR). **Solid lines** represent the solution to the multivariate equation (Appendix), with pulmonary vascular resistance = 2.5 **(upper curve)** and 5.0 **(lower curve)**. The equation is solved for whites with ischemic heart disease undergoing transplantation. **Dashed lines** represent the 70% confidence limits.

Morbid events (Tables 3 to 5). Morbid events were common after cardiac transplantation, with multiple events occurring in many patients (Table 3). Fifty-one episodes of cardiac failure occurred, of which 31% were associated with a fatal outcome. Fifty percent of patients had one or more

Table 3. Morbid Events in 63 Patients After Cardiac Transplantation

General Categories of Morbid Events*	No. of Episodes	Deaths During the Morbid Event†	
		No.	%
Cardiac failure (acute and subacute)	51	16	31
Rejection	49	7	14
Infection	32	5	16
Renal failure	24	0	0
Arrhythmia	16	3	19
Pulmonary failure	16	1	6
Hemorrhage	13	3	23
Behavioral	12	0	0
Metabolic	10	0	0
Neurologic	8	3	38
Gastrointestinal	8	2	25
Liver failure	4	0	0
Hematologic	4	0	0
Sudden death	4	4	100
Bone and joint	1	1	100
Multisubsystem failure	1	1	100

*In many instances, multiple morbid events occurred simultaneously in the same patient; †but not necessarily caused by the specific morbid event.

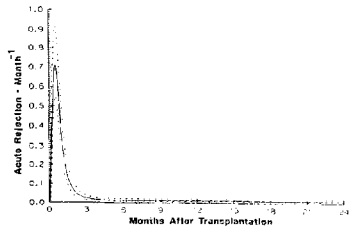

Figure 6. Hazard function (instantaneous risk of the event at all points in time after operation) for the first rejection episode after 63 cardiac transplantations. **Dashed lines** enclose the 70% confidence limits. Patients are censored at retransplantation.

episodes of cardiac failure within the first 3 months after transplantation. The incidence of cardiac failure was highest early after operation, with no further episodes after 15 months. Twenty percent of the episodes of acute cardiac failure were associated with acute rejection (determined by biopsy or autopsy). None of the 25 episodes of acute cardiac failure occurring in the first 10 days after transplantation were associated with rejection, whereas 50% (8 of 16) of such episodes thereafter were rejection related (p for difference = 0.0001).

Thirty-four of the 63 patients experienced 49 acute rejection episodes (Table 4). Over 50% of all rejection episodes were detected during a routine biopsy without other signs or symptoms suggesting rejection (Table 4). The hazard function for the first acute rejection episode increased from a low level early after transplantation to a peak at approximately 1 month after transplantation (Fig. 6). The incidence of rejection episodes/month per patient declined from 0.44 during the first month to 0.18 during the second month; thereafter, the incidence remained nearly constant at approximately 0.02 for the next 22 months. Patients were at greater risk for subsequent rejection for 1 to 2 months after any treated rejection episode (Fig. 7). Seven (14%; confidence limits 9 to 21%) of the 49 acute rejection episodes were fatal, the mode of death being cardiac failure in 6 and sudden death in 1.

Table 4. Rejection Episodes (n = 49) in 34 Patients After Cardiac Transplantation

Reason for Endomyocardial Biopsy	All Rejections
Routine	26
Low ECG voltage	6
Low ECG voltage and malaise	1
S_3 gallop	3
New atrial and ventricular arrhythmias	2
New heart failure	6
Heart failure and fever	2
Heart failure and infection	1
Heart failure, arrhythmias, GI problem	1
Total	48*

*An additional acute rejection episode was identified at autopsy. ECG = electrocardiographic; GI = gastrointestinal; S_3 = third heart sound.

One or more major infections occurred in 22 of the 63 patients (Table 5). The lung was most often affected and accounted for more than half of the infective episodes. A wide variety of bacterial and opportunistic organisms were responsible for infective complications, and the overall associated mortality rate was 16%. The actuarial freedom from one or more major infections was 69% at 1 year, with few episodes of major infection thereafter. The hazard function for the first major infection was low early after transplantation and (as for rejection) was highest at about 1 month.

There was a close correlation between major infections and recent prior augmentation of immunosuppression (at time of original transplantation, during rejection episodes or after retransplantation) (Fig. 8). After any episode of augmented immunosuppression, the risk of infection was highest during the ensuing 2 to 4 months.

Discussion

Survival. The early and late results of cardiac transplantation have continued to improve over the past decade (10–14) and many risk factors have been suggested that

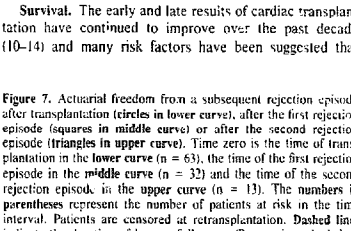

Figure 7. Actuarial freedom from a subsequent rejection episode after transplantation (**circles in lower curve**), after the first rejection episode (**squares in middle curve**) or after the second rejection episode (**triangles in upper curve**). Time zero is the time of transplantation in the **lower curve** (n = 63), the time of the first rejection episode in the **middle curve** (n = 32) and the time of the second rejection episode in the **upper curve** (n = 13). The numbers in **parentheses** represent the number of patients at risk in the time interval. Patients are censored at retransplantation. **Dashed lines** indicate the duration of longest follow-up. Two patients had their first clinical episode of acute rejection after their second cardiac transplantation and are not included here.

Table 5. Major Infections* (n = 32) in 22 Patients After Cardiac Transplantation

Site and Organism	No.	Deaths	
		No.	%
Lung	19	2	11
Pneumococcus	2	0	
Pseudomonas	2	0	
Staphylococcus aureus	1	0	
Mixed flora	3	0	
Legionella	1	0	
Nocardia	4	0	
Mycobacterium	1	0	
Aspergillus	4	2	
Pneumocystis	1	0	
Mediastinal	2	0	0
Enterobacter	1	0	
Staphylococcus aureus	1	0	
Gastrointestinal	2	1	50
Cholecystitis	1	0	
Serratia marcescens	1	1	
Spine	1	0	
Mixed flora	1	0	
Blood	4	0	0
Enterobacter	1	0	
Klebsiella	1	0	
Staphylococcus aureus	1	0	
Candida	1	0	
Brain	1	1	100
Petriellidium boydii	1	1	
Blood plus other organs	3	1	33
Enterococcus	1	0	
Listeria	1	0	
Cytomegalovirus	1	1	
Total	32	5	16 (CL 9 to 25%)

*Includes infections requiring hospitalization and treatment with intravenous antibiotics. CL = 70% confidence limits.

portend a less favorable outcome (15–19). Our finding that the time period of greatest risk is early after transplantation is in keeping with other reports (20), and underscores the importance of avoiding potentially preventable causes of early mortality if late survival is to be improved. Better methods of donor heart preservation (possibly including multidose oxygenated cardioplegia during implantation [21,22] and controlled reperfusion with normothermic hyperkalemic blood [23,24]) and avoidance of serious intraoperative hemorrhage in the presence of multiple previous sternotomies may lessen this early mortality.

The constant phase of hazard (risk) for patients undergoing cardiac transplantation (0.02 death·month^{-1}) is greater than the constant phase hazard of 0.009 for patients with an ejection fraction of 15% undergoing primary coronary bypass surgery at our institution from 1977 to 1981 (25). This suggests that most patients with severe left ventricular dysfunction and severe associated coronary artery disease without a prior sternotomy should undergo coronary revascularization rather than initial transplantation.

Risk factors for death. Subtle immunologic factors that predict irreversible rejection of the transplanted heart would likely represent the most powerful risk factors for premature death if they could be identified. In this study, the only immunologic variable entered into the multivariate analysis was human leukocyte antigen (HLA) compatibility, and that was not significantly related to early or intermediate survival.

Elevated pulmonary vascular resistance has long been identified as an important risk factor (though with limited published data) for early cardiac failure (26), and it was the preoperative risk factor associated with early mortality in this experience. In view of the progressive increase in mortality with increasing pulmonary vascular resistance, special caution is advisable when considering patients for transplantation with even moderate elevation of pulmonary vascular resistance. At the time of transplantation, it may be beneficial to select a larger donor heart with a shorter ischemic time for recipients with elevated pulmonary vascular resistance to maximize the likelihood of robust right ventricular function.

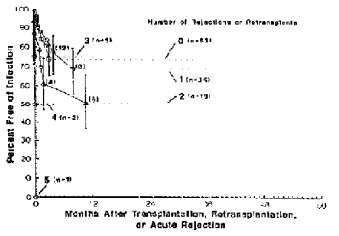

Figure 8. Actuarial freedom from the first major infection after one or more episodes of augmentation of immunosuppression in 63 transplant patients. An episode of augmented immunosuppression may be either treated rejection or retransplantation. *Group 0* (n = 63) (squares) represents the study group after initial transplantation; time zero is the time of initial transplantation. Patients are censored at the time of the first episode of augmented immunosuppression. *Group 1* (n = 35) (circles) represents those patients with one episode of augmented immunosuppression; time zero is the time of the first episode of augmented immunosuppression. Patients are censored at the second episode of augmented immunosuppression. *Group 2* (n = 18) (triangles) represents those patients with two episodes of augmented immunosuppression; time zero is the time of the second episode of augmented immunosuppression. Patients are censored at the third episode of augmented immunosuppression. *Group 3* (n = 5), *Group 4* (n = 2) and *Group 5* (n = 1) are similarly defined. Dashed lines represent the longest additional follow-up of patients at the time of the last actuarial estimate.

Heterotopic cardiac transplantation may also be considered for patients with elevated pulmonary vascular resistance, but the survival rates of the few such patients reported here and the overall survival rates reported in the Registry of the International Society for Heart Transplantation (20) are generally less good than those for orthotopic transplantation. The explanation for increased pulmonary vascular resistance being a risk factor in the constant phase remains obscure.

The identification of cardiomyopathy (versus ischemic heart disease) as a risk factor for late mortality is in contrast with some published data (20,27) indicating improved survival among patients with cardiomyopathy. The reasons for better survival among patients with ischemic heart disease in our experience are unclear. The incremental risk in the late phase associated with black race is also perplexing, but may relate to psychosocial factors, less rigid compliance among some patients or other as yet unidentified factors.

Although the differences in survival between patients maintained on cyclosporine versus azathioprine immunosuppression in this study were not highly significant, the nearly twofold increase in survival to 2 years in patients maintained on cyclosporine is certainly suggestive of a superior immunosuppressive regimen. Results from other centers have been conflicting (28), but the Registry of the International Society of Heart Transplantation (20) has reported a significant ($p < 0.05$) improvement in survival with cyclosporine immunosuppression. The high subsequent mortality in this experience in the small group of patients in whom cyclosporine was completely discontinued and azathioprine initiated (for chronic renal dysfunction) suggests that cyclosporine should be gradually reduced but not eliminated when azathioprine is added because of cyclosporine nephrotoxicity (29). Although not utilized in this experience, a protocol of triple drug immunosuppression, combining cyclosporine, azathioprine and low dose steroids from the time of transplantation, may further increase survival (30).

Morbidity. In the absence of hyperacute rejection, first set cellular-mediated rejection (31,32) is uncommon during the first 5 to 7 days after cardiac transplantation. Indeed, there was no episode of acute cardiac failure associated with acute rejection until after the first 10 days after transplantation. As indicated by the hazard function (Fig. 6), the risk of initial rejection is highest between 2 and 4 weeks after cardiac transplantation, a finding that supports a policy of more intense patient surveillance (currently by endomyocardial biopsy) for possible rejection during the first 1 to 2 months after transplantation. The continuing, though reduced, risk of rejection for at least the first 2 years suggests that scheduled endomyocardial biopsies should be obtained for at least 2 years after transplantation. In view of the increased risk of subsequent rejection within 1 to 2 months of any treated rejection episode, closer patient surveillance and more frequent biopsies are advisable for 1 to 2 months after a rejection episode. A protocol of routine scheduled endomyocardial biopsies is further supported by the observation that more than half the rejection episodes were detected on routine biopsy, without other specific signs or symptoms (Table 6). We do recognize that some controversy exists regarding the intensity of therapy necessary for asymptomatic rejection as diagnosed by endomyocardial biopsy (33,34).

The incidence and types of major infection in our experience were similar to those reported elsewhere (11,28,29,35). The significant mortality rate (16%) associated with major infections underscores the importance of an aggressive diagnostic and therapeutic approach in the immunosuppressed patient. The increased risk of infection after rejection episodes has been noted by others (36), and the analysis presented here indicates that patients are at increased risk for infectious complications for several months after any period of augmented immunosuppression. Surveillance for infection should be particularly emphasized during these periods.

We are indebted to Rob Brown for assistance in data analysis, and to Margie Land, Deb O'Connell and Debbie Ritchey for expert help in data collection. We greatly appreciate the skill of Terri McVay and Grace Williams in preparing the manuscript. We are particularly indebted to John W. Kirklin, MD, FACC for helpful advice throughout the study.

JACC Vol. 11, No. 5
May 1988:917–24

Appendix

Multivariate Analysis for Death at any Time After Cardiac Transplantation

Early phase: Pulmonary vascular resistance (Wood units · m^2) 0.224 ± 0.075, intercept 0.0397.

Constant phase: Pulmonary vascular resistance (Wood units · m^2) 0.298 ± 0.124, morphologic diagnosis of cardiomyopathy (1.27 ± 0.70), black race (1.14 ± 0.54), intercept 0.00139. The shaping parameters were $p = 0.0382$, $\nu = 1.69$, $m = 1$ and $\delta = 0$.

The possible preoperative variables entered into the multivariate analysis included *demographic variables* (age [years] at transplantation, date of transplantation, gender, race); *clinical variables* (New York Heart Association functional class immediately before transplantation and at time of acceptance for transplantation, interval between acceptance and transplantation, catecholamine support at time of transplantation, diagnosis [cardiomyopathy, ischemic heart disease, congenital heart disease], previous surgery); *preoperative cardiac catheterization variables* (left and right ventricular diastolic and systolic pressures [mm Hg], pulmonary artery diastolic, systolic and mean pressure [mm Hg], pulmonary capillary wedge pressure [mm Hg], pulmonary microvascular resistance [Wood units·m^2], cardiac index, ejection fraction); *renal variables* (creatinine [mg/100 ml] and blood urea nitrogen [mg/100 ml] at time of acceptance for transplantation, immediately before transplantation, maximal value during the week before transplantation); *donor heart variables* (gender, race, age [years] of donor, ischemic time of donor heart, recipient-donor sex and race match, human leukocyte antigen compatibility score) and *surgical variables* (surgeon, date of operation, cyclosporine or azathioprine era).

References

1. Cabrol C, Lienhart A, Gandjbakhch I, et al. Choice and handling of donors for cardiac transplantation. Transplant Proc 1984;16:55–6.
2. Davis FD. Coordination of cardiac transplantation: patient processing and donor organ procurement. Circulation 1987;75:I29–39.
3. Rosenthal JT, Shaw BW, Hardesty RL, Griffin BP, Starzl TE, Hakalo TR. Principles of multiple organ procurement from cadaver donors. Ann Surg 1983;198:617–21.
4. Lower RR, Shumway NE. Studies on orthotopic transplantation of the canine heart. Surg Forum 1960;11:18–21.
5. Barnard CN, Losman JG. Left ventricular bypass. South Afr Med J 1975;49:303–12.
6. Novitsky D, Cooper DKC, Barnard CN. The surgical technique of heterotopic heart transplantation. Ann Thorac Surg 1983;36:476–82.
7. Smith SH, Kirklin JK, Geer JC, Caulfield JB, McGiffin DC. Arteritis in cardiac rejection after transplantation. Am J Cardiol 1987;59:1171–3.
8. Billingham M. Some recent advances in cardiac pathology. Hum Pathol 1979;10:367–86.
9. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986;81:615–24.
10. Baumgartner WA, Reitz BA, Oyer PE, Stinson EB, Shumway NE. Cardiac homotransplantation. Curr Probl Surg 1979;16:1–61.
11. Frazier OH, Cooley DA, Pulawin GA, Chandler LB, Okereke OUJ. Cardiac transplantation at the Texas Heart Institute: comparative analysis of 2 groups of patients (1968–1969 and 1982–1983). Ann Thorac Surg 1985;39:303–7.
12. Griepp RB. A decade of human heart transplantation. Transplant Proc 1979;11:285–92.
13. Gandiani VA, Stinson EB, Alderman E, et al. Long-term survival and function after cardiac transplantation. Ann Surg 1981;194:381–5.
14. Griffith BP, Hardesty RL, Thompson ME, Dummer JS, Bahnson HT. Cardiac transplantation with cyclosporine: the Pittsburgh experience. Heart Transplant 1983;2:251–6.
15. Carrier M, Emery RW, Riley JE, Levinson MM, Copeland JG. Cardiac transplantation in patients over the age of 50 years. J Am Coll Cardiol 1986;8:285–8.
16. Emery RW, Cork RC, Levinson MM, et al. The cardiac donor: a six-year experience. Ann Thorac Surg 1986;41:356–62.
17. Hess ML, Hstillo A, Mohanakumar T, et al. Accelerated atherosclerosis in cardiac transplantation: role of cytotoxic B-cell antibodies and hyperlipidemia. Circulation 1983;68(suppl 1):II–1–94.
18. Zusman DR, Stinson EB, Oyer PE, et al. Determinants of accelerated graft atherosclerosis (AGAS) in conventional and cyclosporine treated heart transplant recipients (abstr). Heart Transplant 1985;4:587.
19. Thompson ME. Selection of candidates for cardiac transplantation. Heart Transplant 1983;3:65–9.
20. Solis E, Kaye MP. The Registry of the International Society for Heart Transplantation: third official report—June, 1986. J Heart Transplant 1986;5:2–5.
21. Bodenhamer RM, DeBoer LMV, Geffin GA, et al. Enhanced myocardial protection during ischemic arrest. J Thorac Cardiovasc Surg 1983;85:769–80.
22. Kirklin JK, Shimazaki Y, Digerness SB, Kirklin JW. Emergent surgical revascularization following acute myocardial infarction experimental and clinical considerations. Adv Cardiol (in press).
23. Follette DM, Steed DL, Foslin RP, Key KH, Buckberg GD. Reduction of postischemic myocardial damage by maintaining arrest during initial reperfusion. Surg Forum 1977;28:281–3.
24. Teoh KH, Christakis GT, Weisel RD, et al. Accelerated myocardial metabolic recovery with terminal warm blood cardioplegia. J Thorac Cardiovasc Surg 1986;91:888–95.
25. Kirklin JW, Blackstone EH, Rogers WJ. The plights of the invasive treatment of ischemic heart disease. J Am Coll Cardiol 1985;5:158–67.
26. Griepp RB, Stinson EB, Dong E Jr, Clark DA, Shumway NE. Determinants of operative risk in human heart transplantation. Am J Surg 1971;122:192–7.
27. Hassell LA, Fowles RE, Stinson EB. Patients with congestive cardiomyopathy as cardiac transplant recipients. Am J Cardiol 1981;47:1205–9.
28. Barnhart GR, Hastillo A, Goldman MH, et al. A prospective, randomized trial of prettransfusion/azathioprine/ATG prednisone versus cyclosporine/prednisone immunosuppression in cardiac transplantation: progress report. J Heart Transplant 1985;4(suppl):115.
29. Griffith BP, Hardesty RL, Deeb GM, Starzl TE, Bahnson HT. Cardiac transplantation with cyclosporine A and prednisone. Ann Surg 1982;196:324–9.
30. Andreone PA, Olivari MT, Elick B, et al. Reduction of infectious complications following heart transplantation with triple-drug immunotherapy. J Heart Transplant 1986;5:13–9.
31. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 1944;78:176–99.
32. Hall BM. The cellular immune basis of cardiac allograft rejection. J Heart Transplant 1984;3:260–264.
33. Radovancevic B, Frazier OH, VanBuren CT. Treatment of moderate heart allograft rejection using cyclosporine (abstr). J Heart Transplant 1985;4:618.
34. Michler RE, Smith CR, Drusin RE, et al. Reversal of cardiac transplant rejection without massive immunosuppression. Cardiovasc Surg 1986;74(suppl III):68–71.
35. Dummer JS, Hardy A, Poorsattar J, Ho M. Early infections in kidney, heart, and liver transplant recipients on cyclosporine. Transplantation 1983;36:259–67.
36. Mason JW, Stinson EB, Hunt SA, Schroeder JS, Rider AK. Infections after cardiac transplantation: relation to rejection therapy. Ann Intern Med 1976;85:69–72.